Neural underpinnings of prosexual effects induced by gamma-hydroxybutyrate in healthy male humans

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Neural underpinnings of prosexual effects induced by gamma-hydroxybutyrate in healthy male humans

Running Title
Prosexual effects of gamma-hydroxybutyrate in humans

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ABSTRACT

Gamma-hydroxybutyrate (GHB) is a GHB-/$GABA_B$-receptor agonist currently used as treatment for narcolepsy but also as a drug of abuse. Non-medical GHB users have repeatedly reported prosexual effects including libido-enhancement and lowering of attractiveness standards for partner selection. Here, we examined the putative prosexual effects of oral GHB in healthy males in two experiments both employing randomized, placebo-controlled, double-blind, balanced, and cross-over study designs. In experiment I, subjective effects of 20 and 35 mg/kg GHB vs. placebo were tested in 32 participants using the Sexual Arousal and Desire Inventory. In experiment II, brain reactivity towards erotic vs. neutral pictures was investigated in 15 participants using functional magnetic resonance imaging after 35 mg/kg GHB vs. placebo.

In experiment I, prosexual effects of GHB were shown by increased SADI ratings regarding physiological, evaluative, and motivational aspects of sexual arousal. In experiment II, erotic visual stimuli activated the bilateral insula, nucleus accumbens (NAcc), fusiform gyrus, thalamus, and left occipital pole under placebo. After GHB administration, even sexually neutral pictures of persons induced subjective sexual arousal and increased activation of the bilateral NAcc and right anterior cingulate cortex, which significantly correlated (left NAcc by trend). Moreover, a psychophysiological interaction analysis showed that GHB increased connectivity between NAcc and ventromedial prefrontal cortex during processing of visual erotic cues, i.e., in the condition in which subjective sexual arousal was highest. Our data show that GHB stimulates hedonic sexual functioning and lowers the threshold for erotic perception, which is related with increased susceptibility of mesolimbic reward pathways.

Key words: sodium oxybate, ventral striatum, PPI, reward system, GABA, aphrodisiac, libido, date rape drug

INTRODUCTION

Gamma-hydroxybutyrate (GHB) is an endogenous fatty acid and a metabolite of gamma-aminobutyrate (GABA) (Bessman and Fishbein, 1963). Due to the presence of specific G-protein coupled high and low affinity binding sites and the specificity of the GHB antagonist NCS-382, GHB was postulated to be a neurotransmitter (Benavides et al., 1982; Snead, 2000). Although the physiological role of endogenous GHB is still unclear, some evidence points to neuroprotective, anti-apoptotic activity (Wendt et al., 2014). The compound binds to specific GHB- (Benavides et al., 1982) and $GABA_B$-receptors (Engberg and Nissbrandt, 1993b). However, physiological concentrations of GHB seem to be insufficient to stimulate $GABA_B$ receptors but this mechanism is discussed to be responsible for its psychotropic effects when administered orally in humans (Carter et al., 2009; Engberg and Nissbrandt, 1993a). Furthermore, GHB has neuromodulatory properties on glutamate, dopamine, serotonin, norepinephrine, and acetylcholine neurotransmission (Andresen et al., 2011). Clinically, GHB is internationally approved for the treatment of narcolepsy and in some countries also for the treatment of alcohol withdrawal (Bosch et al., 2012). The drug exerts a broad spectrum of subjective effects, including sedation, stimulation, euphoria, disinhibition, and enhanced vitality (Bosch et al., 2015), for which the drug is instrumentalized by illicit users (Bosch and Seifritz, 2016). Moreover, non-medical users have repeatedly reported prosexual effects of the drug, including increased sexual desire and decreased sexual inhibition (Kapitany-Foveny et al., 2015; Lee and Levounis, 2008; Teltzrow and Bosch, 2012). Consequently, poor decision-making under GHB in erotic situations has been described as “lowering of sexual standards” for partner selection (Palamar et al., 2014).

Neural underpinnings of sexual arousal are commonly studied using functional magnetic resonance imaging (fMRI) and visual erotic stimulation. Processing of visual erotic stimuli without pharmacological challenges was studied in depth, and identified a canonical network consisting of cognitive (anterior cingulate cortex [ACC], fusiform gyrus, parietal cortex, thalamus, insula), emotional (amygdala, insula), motivational (precentral gyrus, ACC, hypothalamus, orbitofrontal cortex [OFC], ventral striatum/nucleus

accumbens [NAcc]), and autonomic (ACC, hypothalamus, thalamus, insula) components (Kuhn and Gallinat, 2011; Stoleru et al., 2012). In contrast, putative prosexual drug effects in humans are not sufficiently studied so far. The indirect dopamine/noradrenaline receptor agonist methylphenidate has been shown to elicit prosexual effects in laboratory settings (Schmid et al., 2015; Volkow et al., 2007), while the exact neural correlates of these effects remain unknown. Moreover, the dopamine D2 receptor agonist apomorphine activates occipitotemporal areas, ACC, and NAcc (Montorsi et al., 2003), as well as the prefrontal cortex (PFC) (Hagemann et al., 2003) during visual erotic stimulation; however, in all of these studies subjective sexual arousal was not assessed.

In order to characterize putative prosexual effects of GHB and associated neuronal underpinnings, we performed two experiments in healthy male volunteers. In the experiment I, subjective effects of GHB were assessed, using the Sexual Arousal and Desire Inventory (SADI) (Toledano and Pfaus, 2006), after oral administration of 20 and 35 mg/kg GHB vs. placebo in a total sample of 32 participants. In experiment II, neural correlates of GHB-induced (35 mg/kg GHB vs. placebo) alterations of the perception of erotic vs. neutral visual stimuli were studied using fMRI in 15 participants. We hypothesized that GHB increases sexual arousal, and that an increased activation of the above mentioned functional network will occur during visual erotic stimulation.

EXPERIMENTAL PROCEDURES

Design and Participants

For both experiments, a randomized, double-blind, placebo-controlled, balanced, crossed within-subject design was used. Participants were heterosexual, non-smoking, healthy males. Thirty-two participants with a mean age of 24.5 years (±3.8 *SD*, range 19-36), a mean verbal intelligence quotient (IQ) of 108.9 (±14.7, 86-145), and a mean weight of 74.9 kg (±8.3, 59-96) took part in experiment one. In experiment two, fifteen participants with a mean age of 23.5 years (±3.6, 20-36), a mean verbal IQ of 113.4 (±18.4, 88-145), and a mean weight of 72.2 kg (±7.4, 59-85) participated. Volunteers were recruited via online advertising and underwent a medical and psychiatric examination applying the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 2002). Exclusion criteria were any DSM-IV psychiatric disorder, neurological disorder, severe medical disease, left-handedness, and regular illegal drug use (lifetime use > 5 occasions, with exception of occasional cannabis use), latter assessed using the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). Moreover, participants were requested to perform the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 2005) to estimate their verbal IQ. Volunteers in experiment 2 were a subsample from experiment 1. They had to abstain from drinking alcohol 24 h before the experiments and from drinking caffeinated beverages on the morning before and during the measurements. Abstinence from illegal drugs was ensured by semi-quantitative drug urine tests (Dimension RXL Max, Siemens, Erlangen, Germany). The study was approved by the Cantonal Ethics Committee of Zurich and by Swissmedic, and was registered at ClinicalTrials.gov (NCT02342366). All participants provided written informed consent and were financially compensated.

EXPERIMENT I

Procedure

Participants randomly received either a low (20 mg/kg, n = 16) or high dose (35 mg/kg, n = 16) of GHB and placebo on two test sessions separated by a seven-day interval. On the experimental days, participants had to fast in the morning before GHB (Xyrem® in orange juice) or placebo (salted orange juice) was orally administered at 9:00 am (t0 min). Experimental sessions lasted for about 225 min. Prosocial and neuroendocrine GHB effects were assessed and published elsewhere (Bosch et al., 2015).

Measures

Sexual Arousal and Desire Inventory

For sexual arousal assessment, we used the German version of the SADI consisting of 53 items (Toledano and Pfaus, 2006), which was applied at time points: t-10 min, t+50 min, t+100 min, and t+150 min. Ratings are done on a 5-point Likert-scale, ranging from 0 ("does not describe it at all") to 5 ("describes it perfectly"). Four scales can be derived from the SADI: *evaluative*, *negative/aversive*, *physiological*, and *motivational* aspects of sexual arousal and desire.

EXPERIMENT II

Procedure

Again, GHB and placebo were applied in two sessions separated by seven days. On both test days, participants completed an fMRI paradigm on a Philips Achieva 3T whole-body MR-unit equipped with a 32-channel head coil (Philips Medical Systems, Best, the Netherlands). The experiment started with a T1-weighted anatomical brain scan, baseline resting-state (rsfMRI), and arterial spin labeling (ASL). Subsequently, participants were taken out of the scanner and were orally administered with a single dose of GHB (35 mg/kg) or placebo (t0 min). As t_{max} of GHB can be expected after about 40 min, the fMRI paradigm began at t+30 min (Liechti et al., 2016). After a post-challenge rsfMRI/ASL scan, participants

underwent the first run of the visual stimulation task (t+48 min). After that, another rsfMRI/ASL scan was performed followed by the second run of the visual stimulation (t+70 min). Subjective drug effects using *Visual Analogue Scales* (VAS) were assessed before visual stimulation (t+46 min) and after stimulation runs (t+55 min and t+77 min) assessing *general drug effect, sedation, relaxation, arousal, euphoria, body sensation, emotionality, sexual arousal, dizziness*, and *nausea.* At the end of the experiment final rsfMRI/ASL scans were assessed again after which participants were taken out of the scanner and debriefed. Experimental sessions lasted for 200 min. VAS data of the items *sexual arousal, arousal, euphoria*, *general drug effect,* and *sedation* will be presented here in relationship to the visual stimulation paradigm. RsfMRI/ASL and remaining VAS data are not related to the present research question and will therefore be published elsewhere.

fMRI task

Participants were presented either neutral or erotic pictures of women or couples during two fMRI runs separated by 22 min resulting in four experimental conditions: *placebo/neutral*, *placebo/erotic*, *GHB/neutral*, and *GHB/erotic* (**Supplementary Figure 1**). One run of the task consisted of a total of 50 pictures presented for 4 s each in a blocked design (10 blocks, 20 s block duration) separated by fixation cross blocks (10 blocks, 20 s block duration). The pictures' order (neutral vs. erotic) was randomized between sessions and participants.

Data Acquisition

Functional time series were acquired with a sensitivity-encoded single-shot echo-planar imaging sequence (SENSE-sshEPI)(Schmidt et al., 2005). The fMRI protocol used the following acquisition parameters: TE=35 ms, TR=2500 ms (=82°), FOV=24 cm, acquisition matrix = 80 x 80 interpolated to 128 x 128, voxel size = 3 x 3 x 3 mm^3, 40 contiguous axial slices (placed along the anterior-posterior commissure plane), and SENSE factor R = 2.0. For structural reference, a 3-dimensional T1-weighted

anatomical scan with the following FFE sequence was obtained: TR/TE = 9.3/4.6 ms, flip angle = 8°, 160 sagittal slices, FOV 240 × 240 mm, voxel size = 1 × 1 × 1 mm^3.

DATA ANALYSIS

SADI data were analyzed using SPSS 22.0 for Windows, applying repeated measures ANOVA with drug (2-fold: GHB vs. placebo) and time (4-fold) as within-subject factors and dose (2-fold: high and low dose) as between-subject factor. Greenhouse-Geisser correction and adjusted p-values were used in models with more than one degree of freedom in the numerator. Uncorrected paired t-tests were applied for post hoc treatment comparisons (placebo vs. GHB). Moreover, VAS data were analyzed by Bonferroni-corrected paired t-tests (4 comparisons: *placebo/neutral* vs *GHB/neutral*, *placebo/erotic* vs *GHB/erotic*, *placebo/neutral* vs *placebo/erotic*, *GHB/neural* vs *GHB/erotic*). All confirmatory statistical comparisons were carried out at a significance level of $p < .05$ (two-tailed).

Imaging data were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK, 2009) implemented in MatLab 2012 (Mathworks Inc., Sherborn, MA). Slice-time correction, unwarping, realignment (b-spline interpolation) and normalization to the standard space of the Montreal Neurological Institute brain (MNI-brain) were performed. Smoothing was conducted with an isotropic 3D Gaussian filter with a full width at half maximum (FWHM) of 6 mm.

On a first level, the functional data were analyzed using the general linear model. The four conditions (*placebo/neutral*, *placebo/erotic*, *GHB/neutral, GHB/erotic*) were modeled in a block design as separate regressors. The six movement parameters estimated in the preprocessing realignment step were entered into all first level models. The voxel-based time series was filtered with a high pass filter (time constant = 128 s). On the group level, a 2 (drug: GHB vs. placebo) x 2 (emotion: erotic vs. neutral) ANOVA was computed in SPM8 to explore main and interaction effects. The threshold for whole-brain analyses was set to $p < .001$ and $k > 15$. Region of interest (ROI) analyses were performed with a threshold of $p < .05$ (family-wise-error; FWE-corrected) and $k > 5$. Masks of the NAcc, the orbitofrontal cortex (OFC), the ACC,

the insula, the thalamus und the occipital cortex were taken from the probabilistic "Harvard Oxford cortical and subcortical structural atlases" provided by the Harvard Center for Morphometric Analysis (25 % threshold)(Kennedy et al., 2016). To further explore the neural correlates of sexual arousal and GHB, BOLD-responses of the contrasts placebo/erotic – placebo/neutral and GHB/neutral – placebo/neutral and were correlated with the respective subjective sexual arousal ratings.

Psychophysiological interaction (PPI) analysis investigates the connectivity between a seed region and other brain areas depending on the psychological variable (the task). The NAcc was selected as seed region due to its crucial impact for the processing of sexual stimuli (Kuhn and Gallinat, 2011; Stoleru et al., 2012). First, the eigenvariate was extracted for the NAcc as implemented in SPM8 for each session (*placebo/neutral*, *placebo/erotic*, *GHB/neutral, GHB/erotic*) separately, because it is not possible to use multiple sessions in a single PPI analysis. After that, the psychophysiological interaction (interaction term) was built by multiplying the extracted eigenvariate (physiological term) with each session separately (the psychological term) and convolving it with the hemodynamic response function. First-level analyses were conducted by creating the contrasts of interest (e.g., GHB/erotic minus GHB/neutral, etc.) using the *imagecalc* procedure of SPM8 for the regressor of interest (PPI regressor). At the second level, we analyzed differences in connectivity between the different sessions (e.g., *GHB/erotic* minus *GHB/neutral*) using one-sample t-tests. Statistical corrections were identical to the previous reported fMRI analyses.

RESULTS

EXPERIMENT I

Sexual Arousal and Desire Inventory

Repeated measures ANOVAs (drug[2] * time[4] * dose[2]) revealed that GHB significantly increased ratings in the scales *physiological* (drug: $F[1,28] = 3.55$, $p = .07$; time: $F[3,84] = 37.2$, $p < .001$; drug * time: $F[3,84] = 9.56$, $p < .001$), *evaluative* (time: $F[3,84] = 31.7$, $p < .001$; drug * time: $F[3,84] = 7.87$, $p < .001$), and *motivational* (time: $F[3,84] = 22.4$, $p < .001$; drug * time: $F[3,84] = 5.28$, $p < .01$) aspects, while the scale *negative/aversive* aspects did not differ (time: $F(3,84) = 1.60$, $p = .21$; drug * time: $F(3,84) = 1.47$, $p = .24$) compared to placebo. Uncorrected post hoc t-tests confirmed significant drug effects at t+50 min for the subscales *evaluative*, and *motivational,* and at t+100 min for the scale *physiological* aspects. As we did not find significant main effects for the factor dose ($p > .25$) on SADI measures, doses are shown pooled in **Figure 1**.

- Figure 1 -

EXPERIMENT II

Subjective Measures

After visual stimulation (t+55 min and t+77 min were pooled), we found that *general drug effect* and *sedation* clearly discriminated GHB and placebo conditions (Bonferroni-corrected paired t-tests: $t(18)=5.94$-6.91, $p < .001$) (**Figure 2a,b**). Moreover, there was an increase of *arousal* and *euphoria* over the four conditions (*placebo/neutral*<*placebo/erotic*<*GHB/neutral*<*GHB/erotic*) (**Figure 2c,d**). GHB clearly increased *sexual arousal* during watching both neutral pictures ($t(18) = 4.03$, $p < .01$) and erotic ($t(18) = 3.22$, $p < .05$) (**Figure 2e**). Additionally, watching erotic pictures increased the *sexual arousal* under placebo ($t(18) = 4.70$, $p < .001$) as well as under GHB ($t(18) = 5.19$, $p < .001$), validating the sexual stimulation paradigm (**Figure 2e**).

- Figure 2 -

Neuroimaging

Because the aim of the study was to explore the impact of GHB on the BOLD-response, we conducted whole-brain analyses as well as ROI-analyses and computed the main effect of GHB and interaction effects. We analyzed the contrast between erotic and neutral pictures in the placebo condition (erotic>neutral under placebo: *placebo/erotic*) and found increased activations in the erotic as compared to the neutral condition in the bilateral insula, bilateral NAcc, bilateral thalamus, bilateral fusiform gyrus, and left occipital pole (see **Table 1**; **Figure 3**). In response to neutral pictures, GHB (GHB>placebo in neutral condition: *GHB/neutral*) elicited significant BOLD response increases in the right ACC and bilateral NAcc (see **Table 1**; **Figure 4**). Most interesting, we found an interaction effect in our ROI-analyses, showing significantly increased BOLD-responses to the bilateral NAcc in the contrast *GHB/neutral* as compared to the *placebo/neutral* condition (**Figure 4c**). In contrast, no increased activation could be found in the opposite contrast *placebo/neutral* >*GHB/neutral*. The comparison of GHB>placebo in the erotic condition (*GHB/erotic*) revealed no significant changes. However, a PPI analysis of the GHB effect on the perception of erotic and neutral pictures revealed an increased task-related functional connectivity between NAcc and the ventromedial PFC (vmPFC) ($p < .05$, FWE-corrected) under the influence of the drug (**Figure 5**). Moreover, correlating BOLD-responses with sexual arousal ratings revealed significant positive correlations between sexual arousal and increased BOLD-responses in the contrast *placebo/erotic – placebo/neutral* in the left (x/y/z= -6/14/-2; z= 3.12, p = .02, FWE-corrected) and right (x/y/z= 6/14/-2; z= 2.99, p= .03, FWE-corrected) NAcc as well as the orbitofrontal cortex (x/y/z= -28/30/-18; z= 4.31, p= .009, FWE-corrected). In the same vein, sexual arousal also positively correlates with BOLD-responses in the contrast *GHB/neutral – placebo/neutral* in the right (x/y/z= 12/16/-4; z= 2.81, p= .05, FWE-corrected) NAcc, the ACC (x/y/z= 14/44/10; z= 4.08, p= .03, FWE-corrected) as well as a marginal trend in the left NAcc (x/y/z= -8/18/-2; z= 2.5, p= .09, FWE-corrected).

- Figures 3, 4, 5 -

DISCUSSION

To our knowledge, the present study is the first investigating the neural effects of GHB using neuroimaging techniques. Our results demonstrate that GHB in fact has prosexual effects in healthy males as the drug increased subjective sexual arousal with and without visual erotic stimulation, respectively. In a sexual stimulation fMRI paradigm, erotic pictures under placebo (*placebo/erotic*) elicited sexual arousal and increased BOLD signals in a neuronal network including the bilateral insula, NAcc, thalamus, fusiform gyrus, and left occipital pole, as expected. Sexual arousal positively correlated with BOLD signals in NAcc and orbitofrontal cortex in this condition. While the combination of GHB and erotic pictures (*GHB/erotic*) did not result in BOLD changes compared to placebo/erotic, we found an increased task-related functional connectivity between the NAcc and the left vmPFC in this condition. However, after GHB intake, the bilateral NAcc as well as the ACC were activated already by sexually neutral pictures of females (*GHB/neutral*), which significantly correlated with increased subjective sexual arousal measured with the VAS (left NAcc by trend). Thus, increased hedonic sexual drive and enhanced erotic perception of neutral stimuli induced by GHB seems to be mediated by increased reactivity of the mesolimbic reward system.

Pleasures of food, sex, and drugs of abuse produce highly overlapping patterns of mesolimbic reward system activation, including the prefrontal cortex, insula, ACC, NAcc, and ventral pallidum (Berridge and Kringelbach, 2015). They are understood to serve adaptive functions by motivating an individual to pursue rewards necessary for fitness. Hedonic gain of function may occur, when the susceptibility of the reward system for erotic or other stimuli is pharmacologically increased. As such, GHB used as a club drug, was reported to increase sexual feelings and to “lower sexual standards” for partner selection (Palamar et al., 2014). Here, in experiment I, GHB increased sexual arousal, resulting in elevated ratings in the SADI-scales *physiological*, *evaluative,* and *motivational* aspects of sexual arousal and desire (**Figure 1a-c**). Moreover, visual stimulation with erotic, but also with neutral pictures of females increased VAS for sexual arousal after GHB intake (**Figure 2e**). Reports of sexual enhancing effects of psychostimulants

were recently confirmed by two experimental studies administering methylphenidate (Schmid et al., 2015; Volkow et al., 2007). The prosexual effects of psychostimulants have been attributed to their capacity to increase dopamine concentrations in the mesolimbic reward system involving dopaminergic neurons in the ventral tegmental area (VTA) that innervate the NAcc, amygdala, and the vmPFC (Frohmader et al., 2010). On the contrary, GHB is a mixed GHB-/$GABA_B$ agonist but its behavioral effects are mediated mostly by GABAergic mechanisms when exogenously applied (Carter et al., 2009). The only GABAergic drug previously discussed as potentially prosexual is alcohol. However, animal and human data have shown opposite effects: sexual disinhibition of low and sexual inhibition of high doses of alcohol (Frohmader et al., 2010). Nevertheless, GHB also has downstream effects on the neurotransmission in the mesolimbic dopamine system (Snead and Gibson, 2005). In the substantia nigra and striatum of rats the occurrence of markers for GHB synthesis indicates GHBergic control of presynaptic dopaminergic activity (Hedou et al., 2000). However, it is a matter of debate if GHB enhances (Cruz et al., 2004) or inhibits (Brancucci et al., 2004) dopaminergic output in terminal regions, and if these effects are mediated by $GABA_B$- or GHB-receptors. Converging evidence points to a dose- and time-dependent bi-directional effect of GHB on mesolimbic dopamine release (Hechler et al., 1991). Lower doses seem to indirectly disinhibit dopaminergic VTA neurons, while increasing doses additionally directly inhibit dopaminergic neurons (Labouebe et al., 2007).

In line with these preclinical findings, erotic pictures in the placebo condition, as well as neutral and erotic pictures in the GHB condition elicited subjective sexual arousal and activated neuronal networks related to sexual arousal and reward processing in our participants (**Figures 2-5**). The networks identified here, highly correspond to a canonical sexual-cue processing circuit previously described in the meta-analyses of Kuhn and Gallinat (2011) and Stoleru et al (2012). Specifically, our patterns cover cognitive (ACC, fusiform gyrus, thalamus, insula), emotional (insula), motivational (ACC, ventral striatum/NAcc), and autonomic (ACC, thalamus, insula) components of sexual arousal outlined by these authors. While activations in the *placebo/erotic* condition could be found in widespread regions confirming earlier

results in this field, GHB-related alterations were specifically located in areas pertaining to the mesolimbic reward system such as the ACC, NAcc, and vmPFC. In fact, the dopamine D2 receptor agonist apomorphine, which is used as second-line treatment for erectile dysfunction, also increased activity in the ACC (Hagemann et al., 2003) and NAcc (Montorsi et al., 2003) in response to visual erotic stimulation. Unfortunately, subjective sexual arousal has not been assessed in this investigation. In our study, subjects under the influence of GHB perceived neutral pictures as sexually arousing, which was correlated with increased activity in the ACC and NAcc compared to placebo.

It has been proposed that the ACC mediates motivational aspects of behavior, including sexual arousal, by modulating reward processing through its projections to the NAcc (Sesack and Grace, 2010; Sewards and Sewards, 2003). It is regarded as a key structure in the processing of the initiation, persistence, and seeking of sexual reward (Frohmader et al., 2010). In humans, the ACC is crucial for the processing of emotional valence of erotic stimuli (Walter et al., 2008). Moreover, reduced ACC responsiveness to erotic stimuli was found under medication with paroxetine, which was paralleled by increased subjective ratings of sexual dysfunction (Abler et al., 2011). In another fMRI study, resting-state functional connectivity reductions of the amygdala with the ACC, dopaminergic midbrain, and insula predicted the occurrence of paroxetine-induced sexual dysfunction, whereby ACC connectivity was correlated with impaired sexual satisfaction (Metzger et al., 2013).

Showing a close functional relationship with the ACC, the NAcc is a converging node for cortical (ACC, vmPFC) and subcortical (VTA) projections, playing an essential role in selecting hedonic motivated behaviors (Sesack and Grace, 2010). NAcc activity is seen as the neural representation of direct reward and reward anticipation (Ponseti et al., 2006; Walter et al., 2008). As such, it forms part of the above mentioned sexual-cue related networks, and was directly associated with the degree of perceived sexual arousal in two studies (Redoute et al., 2000; Walter et al., 2008). On the contrary, reduced NAcc responses to reward are correlated with state anhedonia in patients with depression (Pizzagalli et al., 2009; Wacker et al., 2009) and healthy subjects (Keller et al., 2013). The ROI-based analysis of the NAcc

in our subjects showed that all conditions that induced sexual arousal also increased NAcc activity (*GHB/erotic* only by trend, **Figure 4**).

As expected, the condition *GHB/erotic* led to the highest levels of self-described sexual arousal. While no BOLD changes occurred in this condition compared to placebo, we found an increased task-related functional connectivity between NAcc and left vmPFC using PPI analysis (**Figure 5**). Recently, a growing recognition for task-related functional connectivity changes has been established in psychiatric research (Admon et al., 2015; Cisler et al., 2014; Steuwe et al., 2015), also in absence of direct BOLD alterations (Esslinger et al., 2009). A majority of the neural afferents to the NAcc originates from vmPFC, by which behavioral drives, mood states, direct or anticipated reward shape consecutive behaviors (Sesack and Grace, 2010). Interestingly, NAcc-PFC functional connectivity is reduced by dopaminergic drugs such as methylphenidate (Ramaekers et al., 2013) and pramipexole (Ye et al., 2011) in healthy subjects, pointing to a differential effect of these substances and GHB on brain reward circuits. The increased task-related functional connectivity in the NAcc-vmPFC pathway, together with the GHB-induced enhancement of ACC and NAcc activity demonstrates a pronounced susceptibility of mesolimbic reward pathways towards hedonic stimuli under influence of the drug. Because of this, enhancement of ACC and NAcc activity might be a useful biomarker to assess GHB effects on hedonic/sexual functioning, including potential therapeutic implications for depression treatment and resolution of antidepressant-related sexual dysfunction (Bosch et al., 2012; Bosch and Seifritz, 2016).

Our study bears a number of limitations: the sample size was low and limited to heterosexual male subjects. The latter was owed to the decision to start with one gender and one sexual orientation first. Moreover, due to limited funding we only used one dose in experiment II. Moreover, effectivity of blinding was not systematically assessed, and questionable due to recognizable subjective drug effects. Further studies assessing prosexual effects of GHB should explore gender-, sexual orientation-, and dose-dependent effects, and consider the use of an active placebo to reduce probability of unblinding.

In summary, our primary finding is that GHB induces subjective sexual arousal and lowers the threshold for erotic perceptions probably by altering the reactivity of mesolimbic brain networks. Thus, under GHB, even non-erotic stimuli can induce sexual arousal and a sexual-cue related brain activation pattern including ACC and NAcc. Additionally, the drug increases NAcc-vmPFC functional connectivity during processing of visual erotic cues, which was paralleled by the highest scores of subjective sexual arousal. The study therefore confirms at an objective, controlled, and experimental level the reports of recreational users that GHB leads to enhanced sexual arousal and less selective sexual partner choice. The observed prosexual effects are most likely induced by GHB- and/or $GABA_B$-receptor-mediated disinhibition of VTA neurons, resulting in increased dopamine release in the NAcc, ACC, and vmPFC.

AUTHOR DISCLOSURES

Role of Founding Source

The study was in part supported by funds of the Clinical Research Priority Programs ‘Sleep and Health’ and 'Molecular Imaging' of the University of Zurich. The University of Zurich did not influence the study design, and the collection, analysis and interpretation of the data.

Contributors

Oliver G. Bosch, Katrin H. Preller, Marcus Herdener, Rainer Kraehenmann, Philipp Staempfli, Milan Scheidegger, Erich Seifritz, and Boris B. Quednow designed the study and wrote the protocol. Oliver Bosch, Michael Havranek, Andrea Baumberger, and Robin von Rotz managed the literature searches and analyses. Michael Havranek, Milan Scheidegger, and Tim Klucken undertook the statistical analysis, and Oliver Bosch and Boris B. Quednow wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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Tables

Table 1 Peak MNI coordinate regions with significant BOLD signal changes (p<0.05, FWE-corrected, k=15)

Peak MNI coordinate regions	Laterality	Cluster size	Laterality (MNI)			zmax	pcorr	Figure
			X	Y	Z			
Erotic > neutral in the placebo condition								
Insula	L	23	-36	-4	16	3.86417	0.0144199	3a
Insula	R	378	38	-8	0	3.47669	0.0499014	
Nucleus Accumbens	L	31	-6	14	-2	2.94016	0.0265744	3b
Nucleus Accumbens	R	40	6	14	-4	2.74202	0.0442265	
Thalamus	L	422	-16	-14	4	3.69614	0.023752	3c
Thalamus	R	400	12	-12	2	3.95807	0.00974635	
Fusiform Gyrus	L	476	-40	-66	-10	4.61506	0.0006029	3d
Fusiform Gyrus	R	307	42	-64	-12	3.97446	0.00666532	
Occipital Pole	L	257	-32	-90	22	4.40386	0.00753929	3e
GHB > placebo in the neutral condition								
Anterior Cingulate Cortex	R	534	2	26	16	3.98933	0.0178517	4a
Nucleus Accumbens	L	18	-10	18	-4	3.18159	0.0135556	4b
Nucleus Accumbens	R	34	12	18	-4	2.91162	0.0286576	
GHB > placebo in the erotic condition								
No significant changes found								

Figure Legends

Fig. 1: Ratings (means and SEM) of the scales *physiological* (a), *evaluative* (b), *motivational* (c), and *negative/aversive* (d) aspects of the Sexual Arousal and Desire Inventory (SADI) after GHB compared to placebo. Paired t-tests (uncorrected): *p<.05, **p<.01.

Fig. 2: Visual analogue scale (VAS) ratings after visual stimulation task (t+55min and t+77min were pooled) in the conditions placebo/neutral, placebo/erotic, GHB/neutral, and GHB/erotic: a) general drug effect, b) *sedation*, c) *arousal*, d) *euphoria*, and e) *sexual arousal*. Paired t-tests (Bonferroni-corrected): *p<.05, **p<.01, ***p<.001.

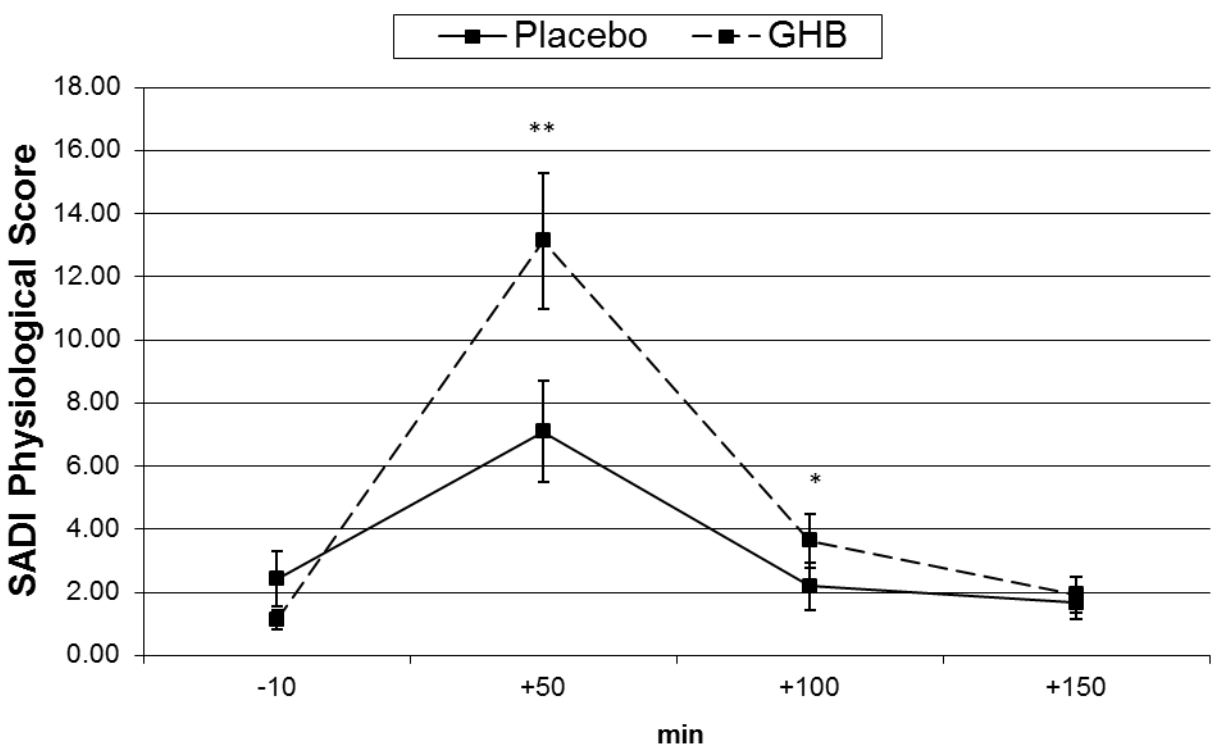
Fig. 3: Axial BOLD response whole-brain map of the contrast placebo/erotic – placebo/neutral (*placebo/erotic* condition): a) insula, b) nucleus accumbens, c) thalamus, d) fusiform gyrus, e) occipital pole (p<.05, FWE-corrected, k=15).

Fig. 4: BOLD response whole-brain map of the contrast GHB/neutral – placebo/neutral (*GHB/neutral* condition): a) anterior cingulate cortex, b) nucleus accumbens (p<.05, FWE-corrected, k=15), and c) region of interest (ROI) BOLD signal comparison of the four assessed conditions in the nucleus accumbens (*=p<.05, FWE-corrected).

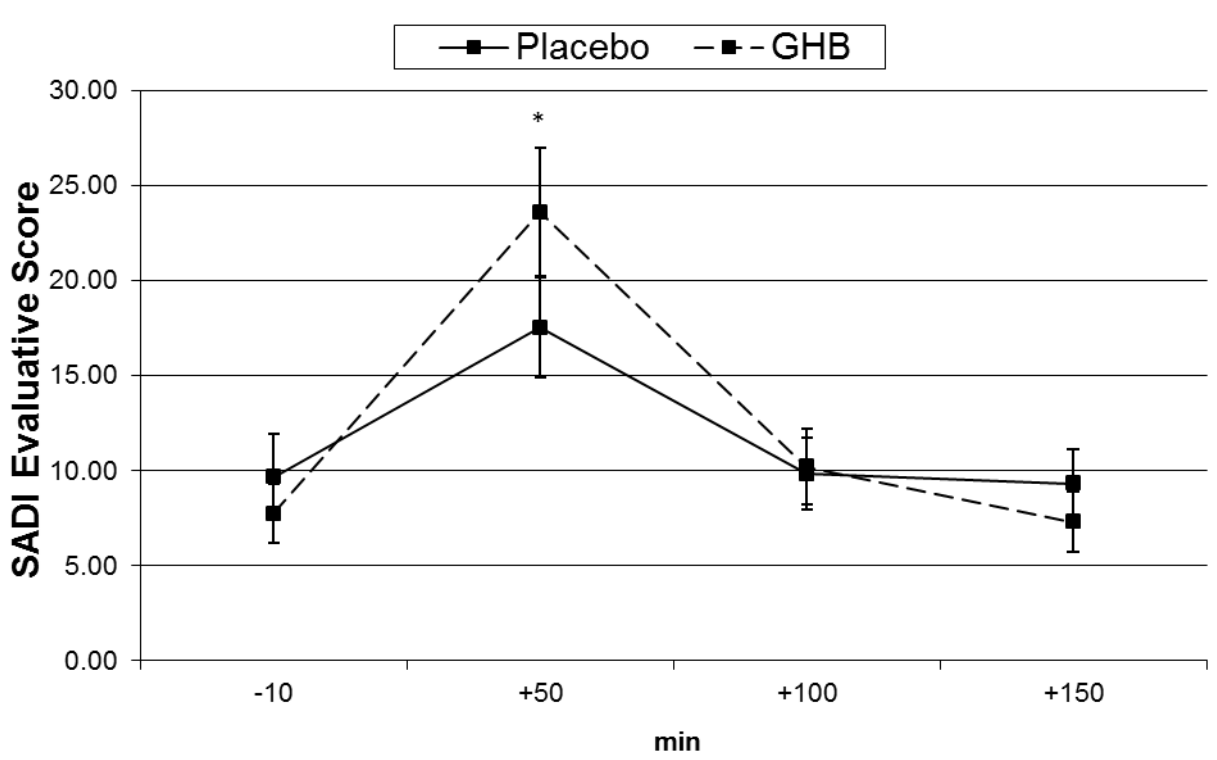
Fig. 5: Psychophysical Interaction of GHB and erotic pictures on task-related connectivity of nucleus accumbens with left ventromedial prefrontal cortex (*=p<.05, FWE-corrected).

Figure 1

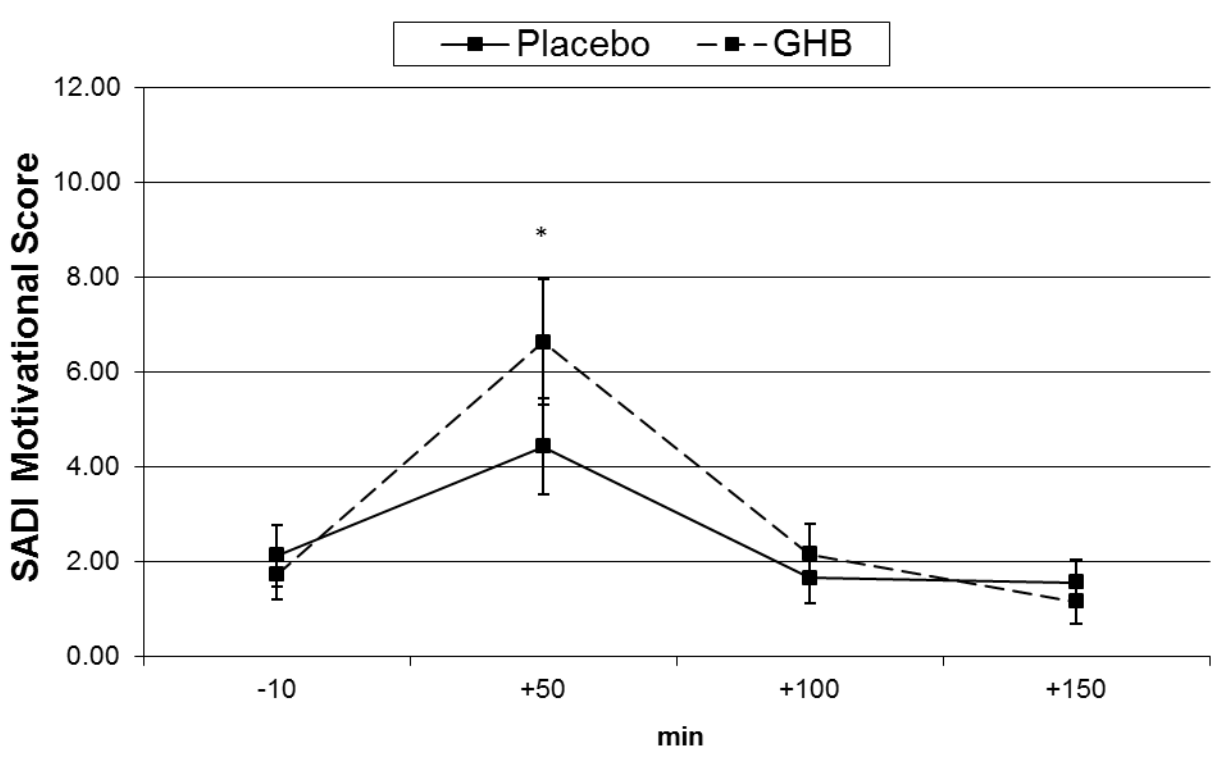
(a)



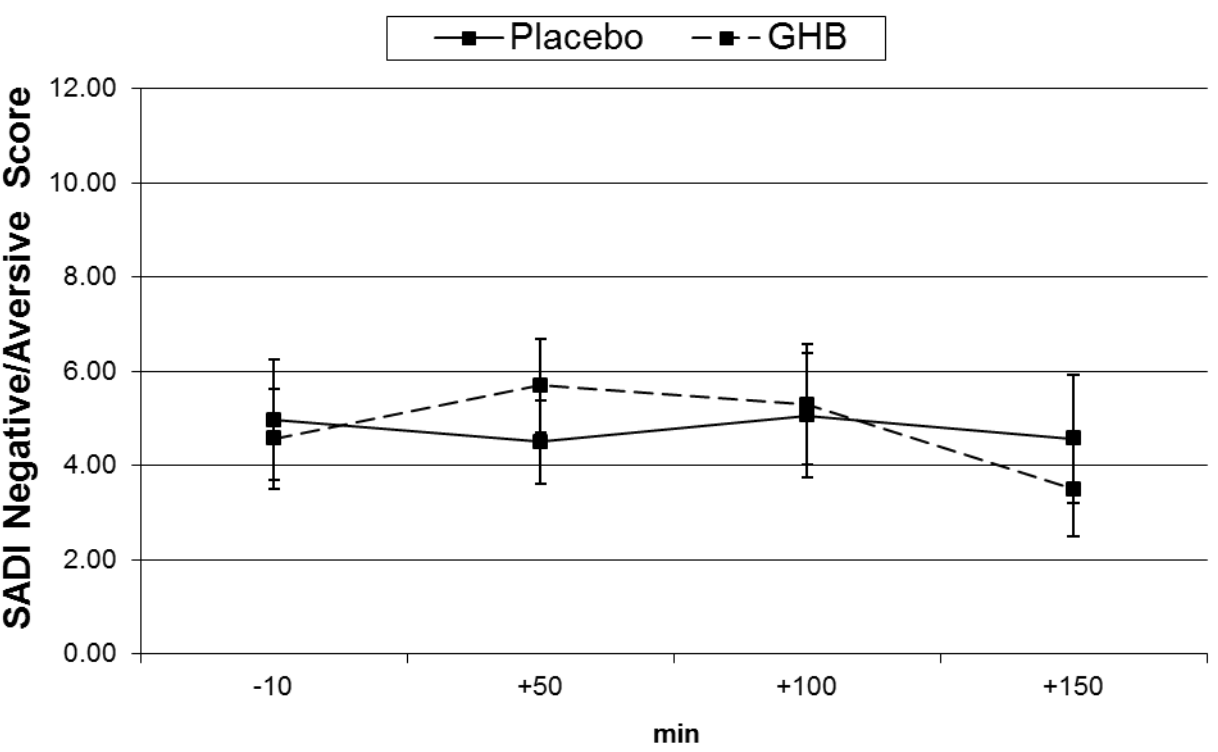
(b)



(c)

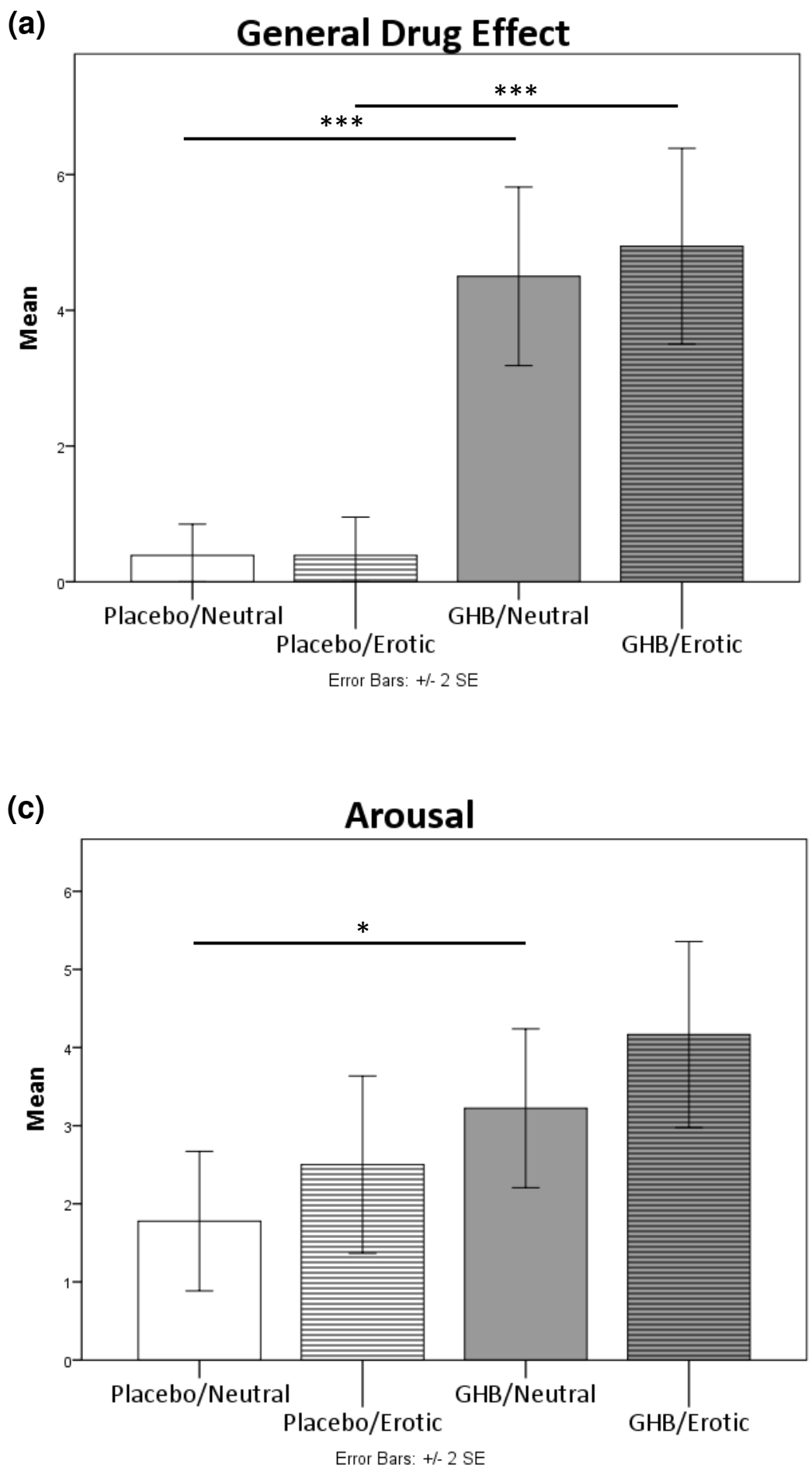


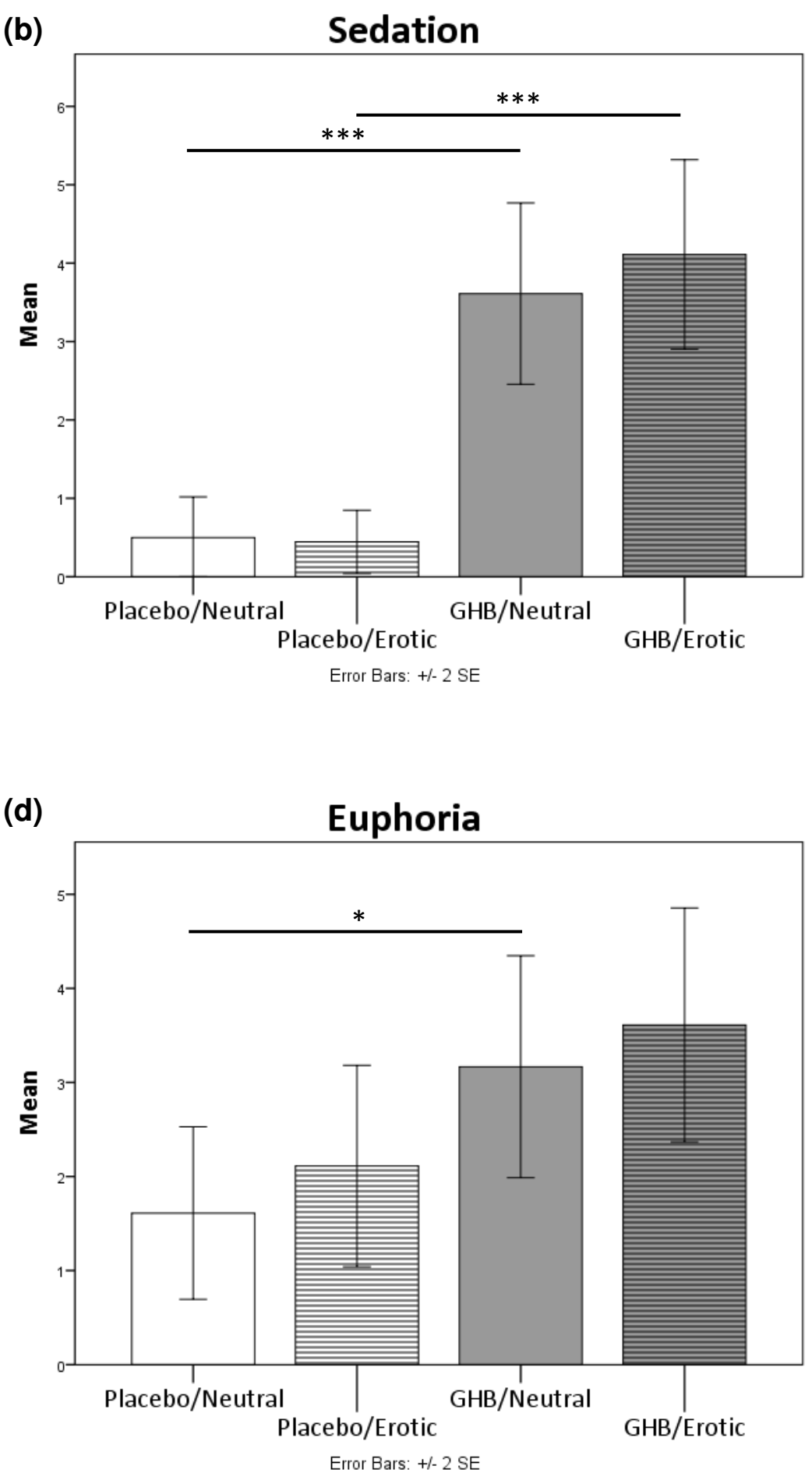
(d)

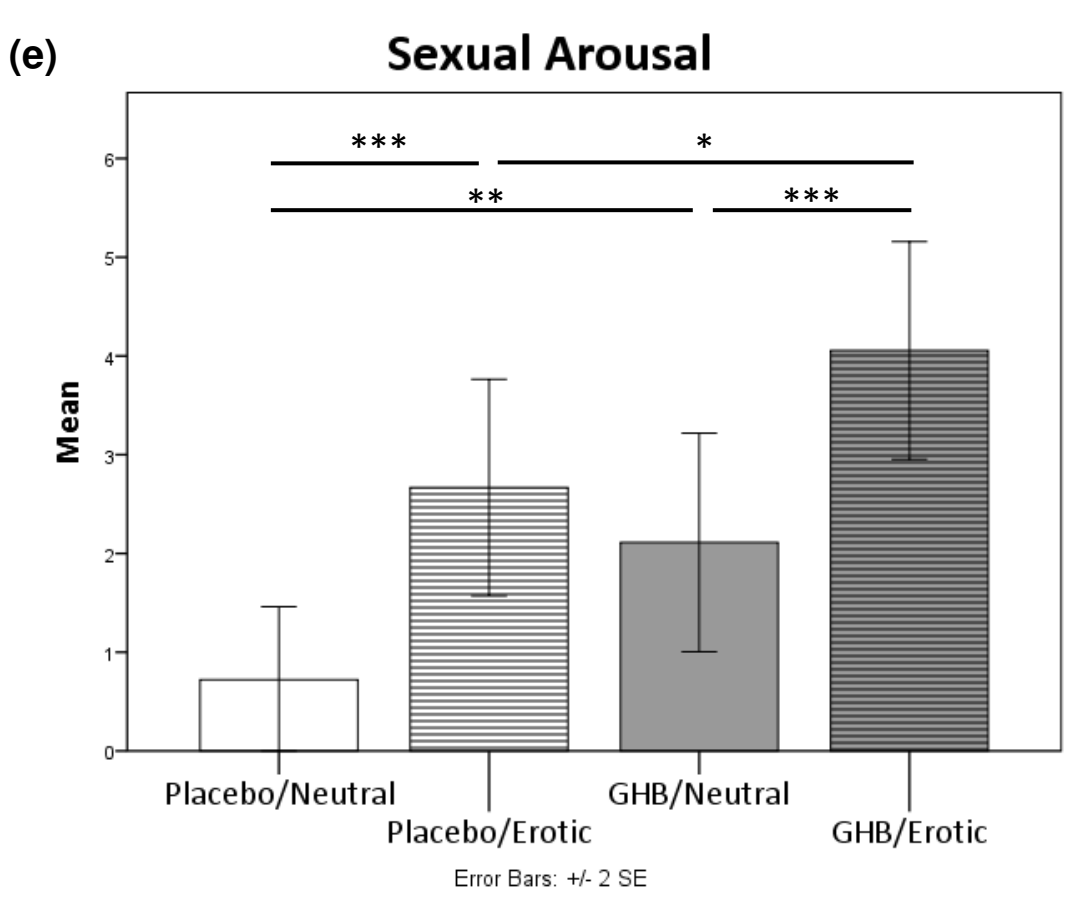


Figure(s)

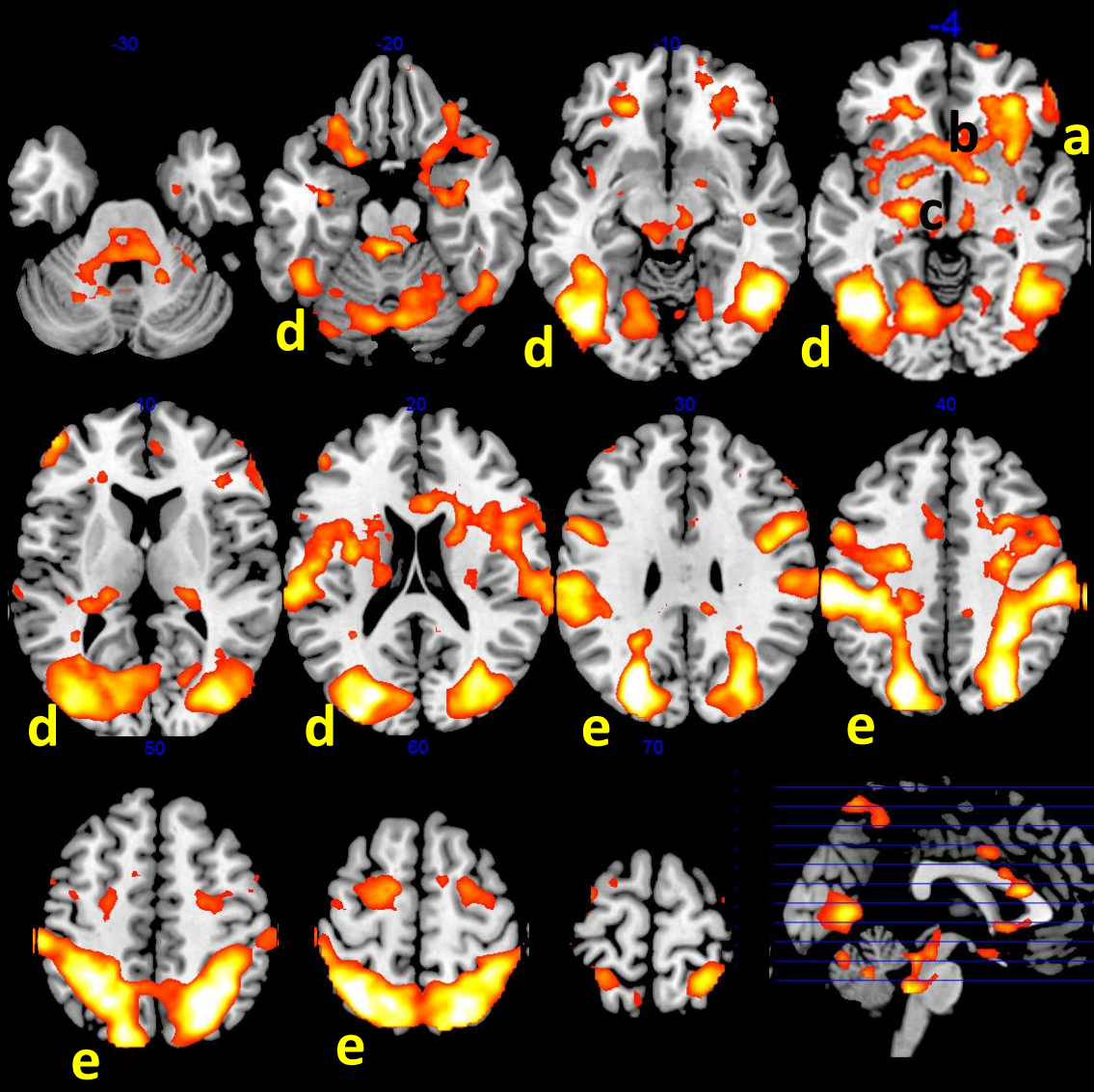
Figure 2



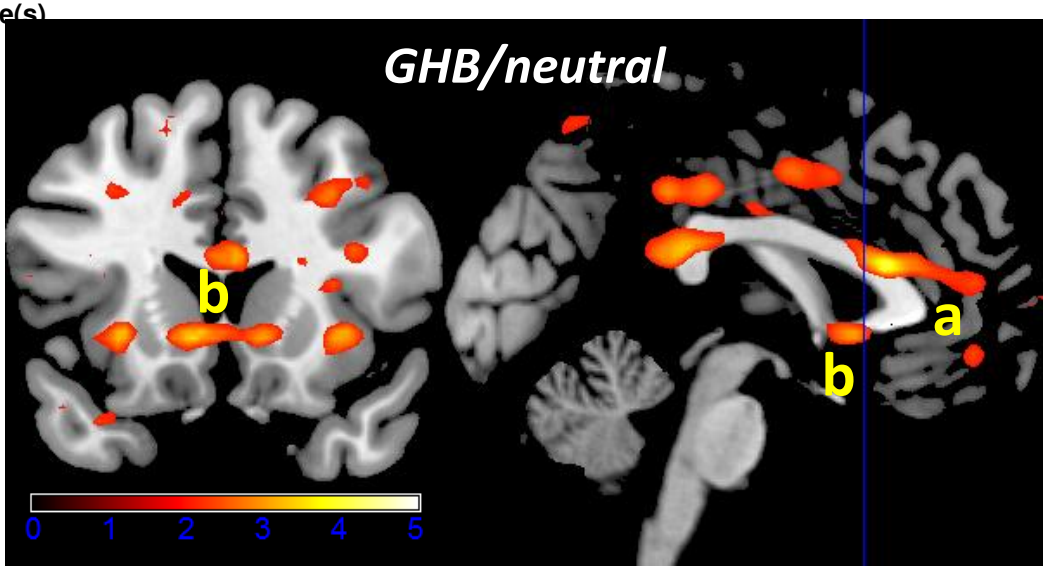




Placebo/erotic



Figure(s)


GHB/neutral
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1
2
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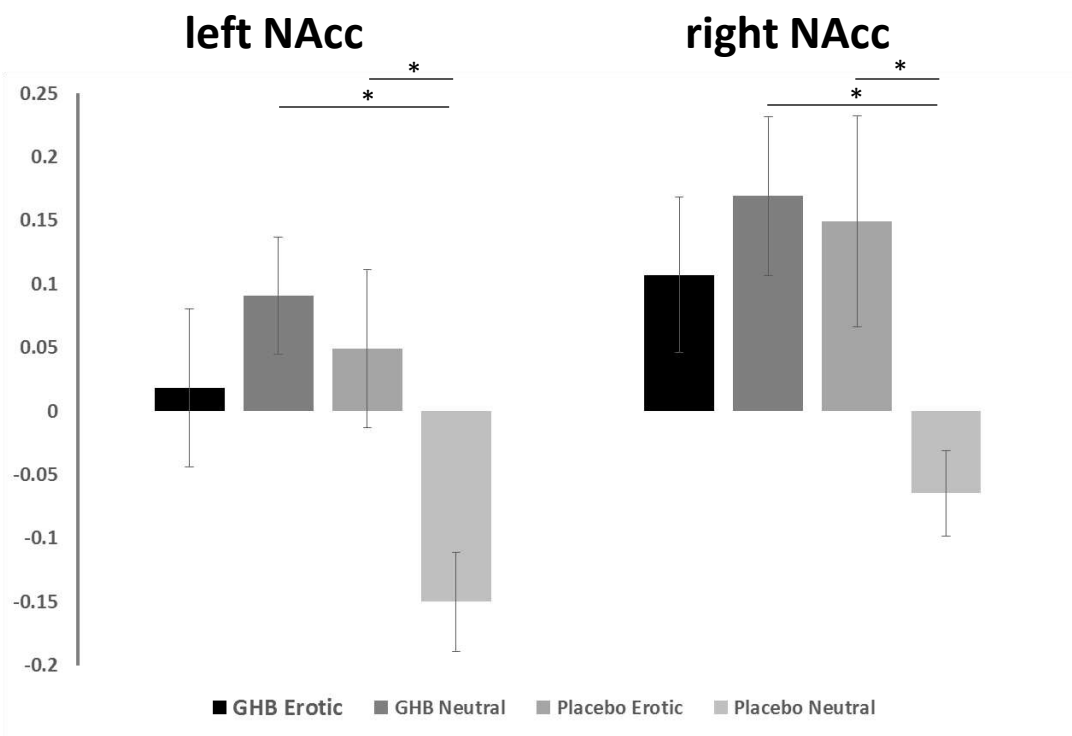
5

c)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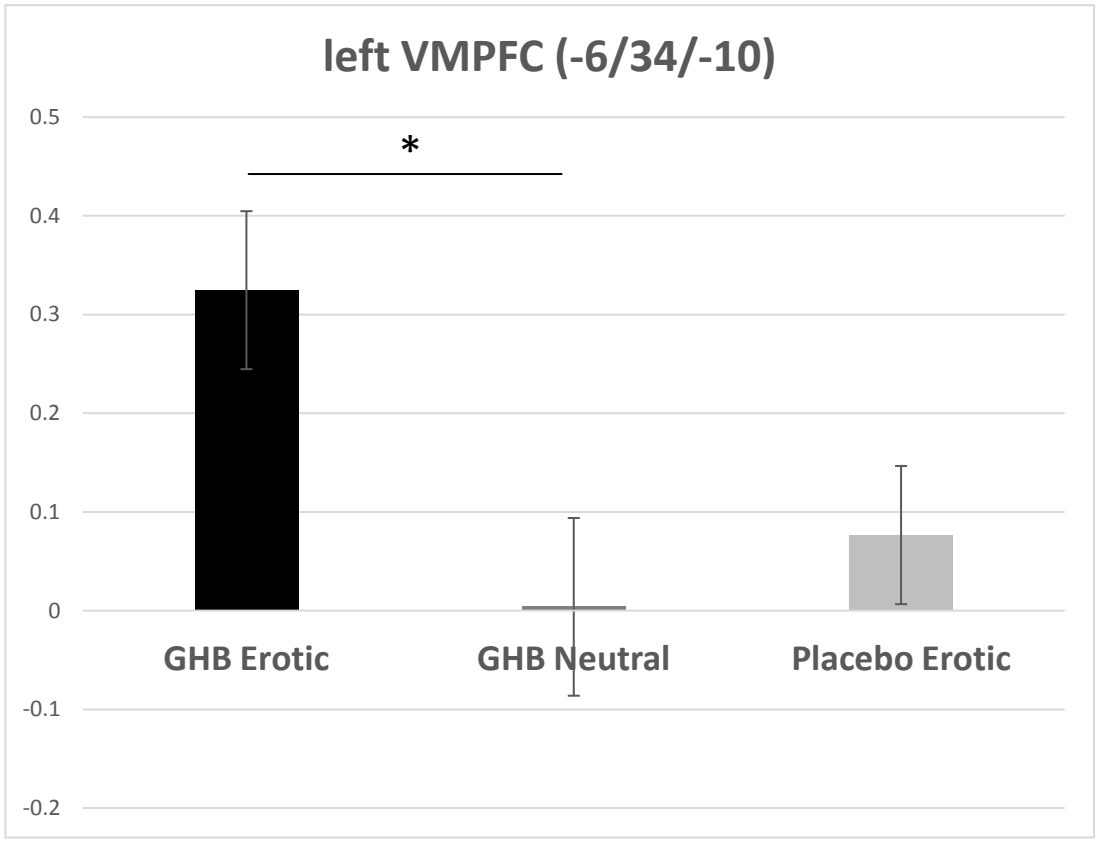
GHB Erotic
GHB Neutral
Placebo Erotic
Placebo Neutral

Figure(s)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*
GHB Erotic
GHB Neutral
Placebo Erotic

***Role of the Funding Source**

Role of Founding Source

The study was in part supported by funds of the Clinical Research Priority Programs ‘Sleep and Health’ and 'Molecular Imaging' of the University of Zurich. The University of Zurich did not influence the study design, and the collection, analysis and interpretation of the data.

Contributors

Oliver G. Bosch, Katrin H. Preller, Marcus Herdener, Rainer Kraehenmann, Philipp Staempfli, Milan Scheidegger, Erich Seifritz, and Boris B. Quednow designed the study and wrote the protocol. Oliver Bosch, Michael Havranek, Andrea Baumberger, and Robin von Rotz managed the literature searches and analyses. Michael Havranek, Milan Scheidegger, and Tim Klucken undertook the statistical analysis, and Oliver Bosch and Boris B. Quednow wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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Supplementary Material

Click here to download Supplementary Material: 03 Bosch Havranek et al 2016 SUPP_FINAL.docx

SUPPLEMENTARY MATERIAL

Neural underpinnings of prosexual effects induced by gamma-hydroxybutyrate in healthy humans

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Supplementary Figure 1 Examples of pictures from the International Affective Picture System (IAPS) used for the visual stimulation fMRI paradigm

Neutral	Erotic